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(54) **Radiopaque cyanoacrylate compositions.**

(57) Radiopaque cyanoacrylate compositions for use in industrial and medical applications, e.g. to form welds, seams or plugs, comprise a cyanoacrylate monomer and a radiopaque additive stable to the monomer. The additives may be organic iodo compounds or certain cyanoacrylate stable inorganic compounds. Organic iodoacids can serve the additional function of an anionic inhibitor for the monomer. The compositions may be inspected in situ with X-rays.

EP 0 050 457 A1

RADIOPAQUE CYANOACRYLATE COMPOSITIONS

Methyl cyanoacrylate (MCA) and other cyanoacrylates are well known chemical products which have found wide use in industry and in the medical field for a variety of purposes, e.g. as a tissue adhesive.

Thus, the ability of the alkyl 2-cyanoacrylate to polymerize rapidly at room temperature in the absence of a solvent or added catalyst has resulted in the use of this class of monomers for surgical application. 2-cyanoacrylate monomers have been used as physiological adhesives in bronchial closure, the anastomosis of small arteries, intestinal anastomosis and cutaneous lacerations. Methyl cyanoacrylate has found application in the field of permanent sterilization of human females. Sterilization of the female is accomplished by introduction of small quantities of MCA into the fallopian tubes wherein contact with body moisture polymerizes the MCA and blocks the fallopian tube. With passage of time, fibrous tissue growth replaces the MCA and permanent sterilization results. This latter use and procedure is described in U.S. Patent No. 3,822,702 and 3,948,259.

For some of the medical applications of the cyanoacrylates, it is desirable that there be some means for inspecting the result of the surgical operation without the need for surgically reopening the patient. For instance, in the anastomosis of arteries or intestines, it is desirable to have some means for non-intrusively inspecting the joined tubes in order to verify that a proper weld has taken place without blockage of the tube. Conversely, where MCA is used to sterilize females it is desirable to inspect the polymer plug to insure that tube blockage has been successfully accomplished.

Cyanoacrylates are also used industrially as adhesives, e.g. for wood, metal, plastic or ceramic parts, and in these applications it is also desirable to be able to inspect the product, particularly for example in the case of hidden seams, welds or plugs.

If the cyanoacrylate ester is made radiopaque, the desired inspection may be accomplished by x-ray of the affected area. However, the polymerization properties which make cyanoacrylates esters useful in medical applications have heretofore prevented formulation of radiopaque compositions. The highly unstable cyanoacrylate esters polymerize under many conditions including exposure to even trace amounts of moisture, oxygen, heat, high energy radiation and active organic sites to note a few. As a result, many of the known radiopaque materials commonly used in other medical applications cannot be incorporated into the monomer as a radiopaque additive for cyanoacrylate esters. Most radiopaque materials reduce the stability of the esters and in some cases even initiate polymerization thereof. In particular, it has been found that organic iodo compounds commercially available as x-ray screening agents are frequently available as sodium salts of a carboxylic acid or as compounds containing primary or secondary amino groups. These materials are not stable to cyanoacrylates and cause polymerization thereof.

The present invention discloses a group of compounds which may be added to methyl cyanoacrylate and other cyanoacrylate esters in order to provide radiopaque compositions useful in medical and industrial applications where it is desired to inspect an adhesive weld or a polymer plug by x-ray techniques. The compositions generally comprise an alpha-cyanoacrylate ester and a radiopaque additive stable to such ester. Radiopaque additives useful in the present invention include organic iodo compounds and certain cyanoacrylate stable inorganic compounds. Certain of the radiopaque additives may be dissolved in the cyanoacrylate ester or in other cases may be employed as a suspension of finely divided additive particles in the cyanoacrylate ester. Organic iodo acids also serve the additional function of an anionic inhibitor which may replace all or some of the inhibitor ordinarily employed in cyanoacrylate medi-

cal compositions. The iodo compounds specifically disclosed herein are listed in the Merck index, Chemical Abstracts or Physicians Desk Reference or are easily convertible derivatives of such listed compounds eg., amines have been alkylated
5 and carboxylic acid sodium salts have been converted to the free acid or an ester. Therefore, physiological data is available on the body compatibility of the compounds disclosed or of closely related derivatives and will not be discussed herein. The term "body compatible" is used to
10 indicate that the additives of the present invention do not cause short term rejection of the cyanoacrylate compositions of the present invention, do not otherwise cause the cyanoacrylate composition to become significantly toxic under conditions of use and that the additive will eventually
15 be eliminated from the body. The compositions thus remain physiologically acceptable.

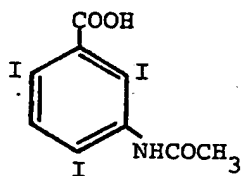
With respect to the organic iodo compounds, it has been discovered that iodo acids including both carboxylic acids and phenols, as well as sterically hindered tertiary
20 amines and carboxylic acid esters are compatible with cyanoacrylate esters. It is further been discovered that soluble iodo carboxylic acids and phenols act as anionic inhibitors, increasing the stability of the composition and, in some cases, replacing conventional inhibitor systems for
25 cyanoacrylates.

The radiopacity of the organic iodo compounds is directly related to the number of iodine atoms in the molecule. For deep body work, the cyanoacrylate composition should contain $.05 \pm .01$ moles of iodine atoms per
30 mole of cyanoacrylate. Consequently, the higher the percentage of iodine in an additive molecule, the lower the amount of the additive necessary in order to achieve the desired radiopacity. For this reason multi-iodo compounds are preferred over mono-iodo compounds. For more superficial
35 applications much less radiopacity is required and, therefore, mono-iodo compounds, or lower amounts of poly-

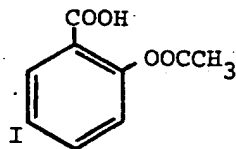
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iodo compounds may be used.

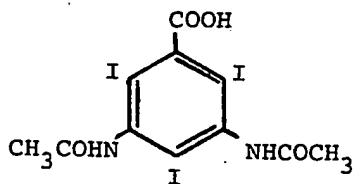
5 Examples of iodocarboxylic acids, soluble in methyl 2-cyanoacrylate, which act as inhibitors as well as radio-paque agents are as follows (the formulas depicted herein control if there is any ambiguity between name and structure; the symbol ϕ designates phenyl):



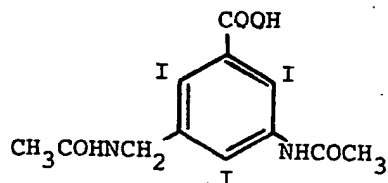
3-acetamido-2,4,6-triodobenzoic acid



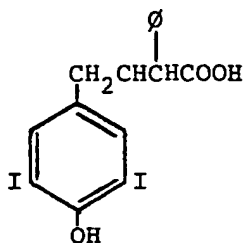
acetyl-5-iodosalicylic acid



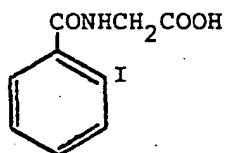
3,5-diacetamido-2,4,6-triodobenzoic acid



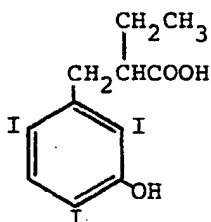
iodamide



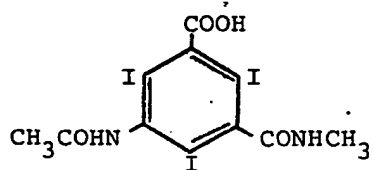
iodoalphonic acid



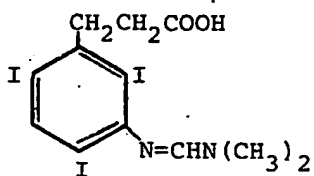
o-iodohippuratic acid



iophenoic acid

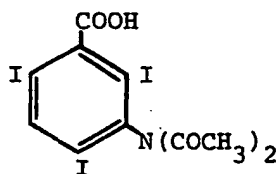


iothalamic acid

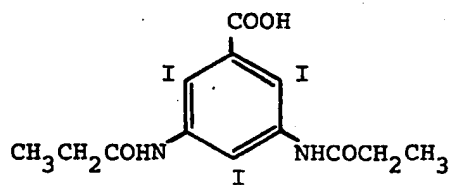


3-[(dimethylaminomethylene)amino]-
2,4,6-triodohydrocinnamic acid

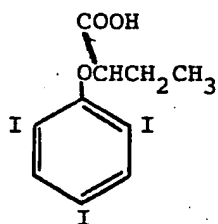
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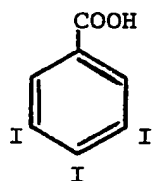
3-(diacetylamino)-2,4,6-triodo-
benzoic acid



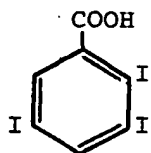
2,4,6-triodo-3,5-dipropiona-
midobenzoic acid



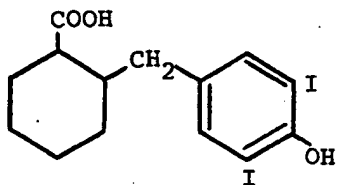
phenobutiodyl



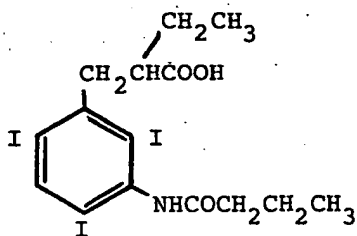
3,4,5-triodo-benzoic acid



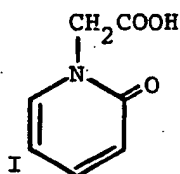
2,3,5-triodo-benzoic acid



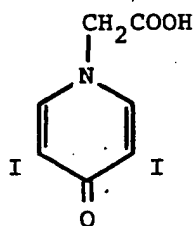
2-(4-hydroxy-3,5-diiodobenzyl
cyclohexane carboxylic acid



3-butylamido- α -ethyl-2,4,6-
triiodohydrocinnamic acid



5-iodo-2-oxo-1(2H)-pyridine
acetic acid



3,5-diiodo-4-oxo-1(4H)-pyridine
acetic acid

Also useful as anionic inhibitors are iodophenols such as 2,4,6-triiodophenol.

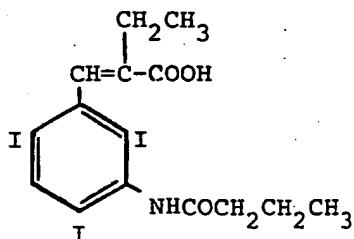
The use of iodocarboxylic acids or iodophenols in the compositions of the present invention is especially advantageous because such use permits the elimination of other inhibitors. This simplifies the complexity of the cyanoacrylate system and, in turn, simplifies the study of the biodegradation of the polymer system and reduces risk of unexpected side effects.

The wide variety of iodocarboxylic acids and phenols useful in the present invention permits the optimization of inhibition and radiopacity according to the particular application of the composition. For adhesive applications where relatively rapid polymerization is required, the radiopaque acids selected will typically have a higher ratio of iodine to acid group (carboxylic acid or phenol) than those used in fallopian tube closure applications where slower polymerization is acceptable and sometimes desirable. Generally, the higher the ratio of iodine to acid group, the less the inhibition at a given level of radiopacity.

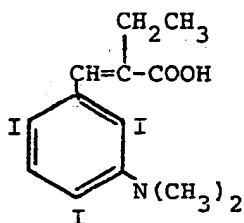
Some carboxylic acids useful in the present invention are not sufficiently soluble in the cyanoacrylate to fully inhibit the polymerization thereof. These later compounds may nonetheless be employed in the compositions of the present invention as suspensions of finely divided acid in the cyanoacrylate. Additional inhibitors may be added to these compositions as required. It is known, for instance, to use SO_2 and antioxidants such as hydroquinone, butylated hydroxytoluene, butylated hydroxyanisole and hydroquinone monomethyl ether as cyanoacrylate inhibitors. For female sterilization applications, compositions utilizing a combination of SO_2 , antioxidants and carboxylic acids such as acetic acid or benzoic acid may be used. These latter compositions are described in co-pending application, Serial No. 74,664.

Examples of carboxylic acids, partially soluble in MCA, which may be used in the compositions of the present invention as radiopaque agents and to partially fulfill

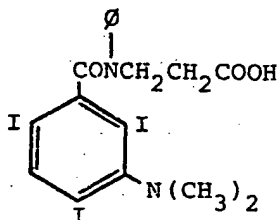
the function of anionic inhibitor, are as follows:



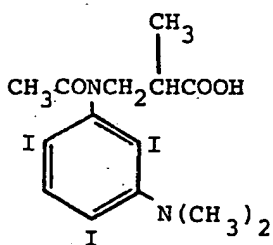
3-butyramido- α -ethyl-2,4,6-tri-
iodocinnamic acid.



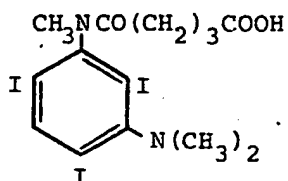
3-dimethylamino- α -ethyl-2,4,6-
triiodocinnamic acid



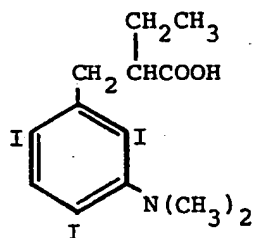
N-(3-dimethylamino-2,4,6-triodo-
benzoyl)-N-phenyl- β -alanine



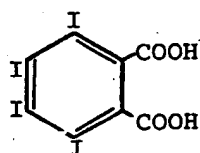
N,N-dimethyl iocetamic acid



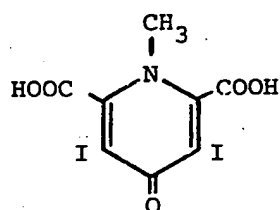
N,N-dimethyl iomeglamic acid



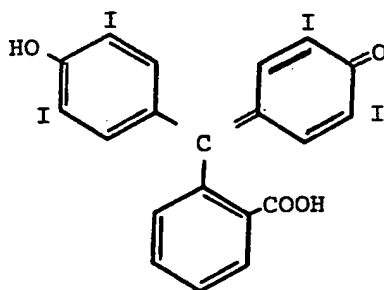
N,N-dimethyl iopanoic acid



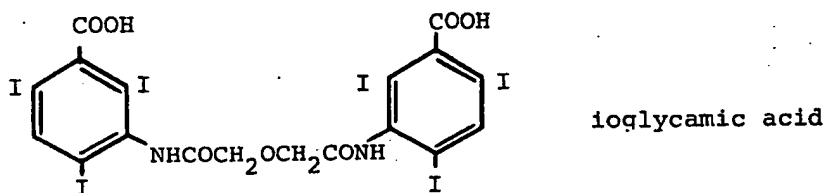
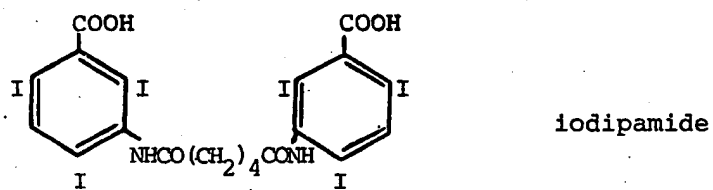
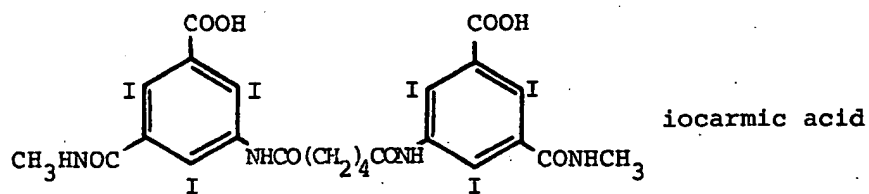
tetraiodo phthalic acid



1,4-dihydro-3,5-diiodo-1-methyl-4-oxo-2,6-pyridine dicarboxylic acid



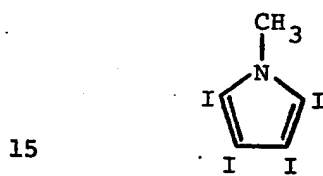
iodophthalein



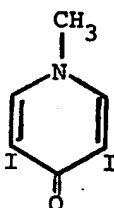
Half esters of the dicarboxylic acids listed above are also useful as soluble or partially soluble iodoacids.

The compounds of an additional class of iodo organics useful in the present invention are neutral to cyanoacrylate, that is they do not act as anionic inhibitors or as polymerization initiators. Esters of the acids listed above are such compounds. Alkyl esters, at least up to and including the pentyl series of isomers, generally have increasing solubility with increased carbon atoms. Other neutral compounds useful in the compositions of the compositions of the present invention are:

iodomethanes such as iodoform and tetraiodomethane; iodothiophenes such as tetraiodo thiophene; and tertiary substituted iodo amines such as:



N-methyltetraiodo pyrrole; and



N-methyl-3,5,diiodo-4(1H)pyridone.

As with the partly soluble acids, compositions utilizing radiopaque agents neutral to cyanoacrylate monomer may require additional polymerization inhibitors.

The final category of radiopaque agents, useful in the compositions of the present invention, comprises certain radiopaque inorganic compounds which have proved neutral to methyl-2-cyanoacrylate. These compounds are completely insoluble in methyl cyanoacrylate but may be employed as suspensions of finely ground particles in the

cyanoacrylate. The inorganic compounds in this category are barium sulfate (BaSO_4) bismuth (Bi), cadmium tungstate (CdO_4W) and calcium tungstate (CaO_4W).

While it is possible to use the materials disclosed herein as suspensions in cyanoacrylate esters, it is much preferred that the additive be completely dissolved in the ester. Complete solution assures accuracy and reproducibility of the additive concentration. Additionally, in some cases, particulate matter in the composition may reduce shelf life.

It has also been found that in some deep body work it is necessary that iodine have a concentration even greater than 5 mole percent. In particular, in female sterilization applications, when attempting to locate the image of a fallopian tube polymer plug against the substantially opaque background of the pelvis, it has been found that a concentration of iodine atoms of about 7 mole percent is desirable in order to obtain a recognizable image. Many of the radioactive additives disclosed herein are not soluble in MCA at this level of concentration. This problem can be overcome if a plurality of stable iodine containing materials are dissolved in MCA. In order to increase total iodine concentration and the composition, these materials must have essentially independent solubilities in MCA or form a complex which itself is more soluble in MCA than the individual additives.

An especially useful composition of this type is a heated equimolar mixture of triiodophenol and iodoform. Iodoform efficiently adds iodine to the cyanoacrylate compositions but does not remain in solution at levels adequate for female sterilization work. Triiodophenol is a preferred additive because it has a relatively high iodine content along with an inhibition function. Also, both compounds have been well studied from a toxicological standpoint and are known to be relatively non-toxic.

EXAMPLE

A mixture of sterile redistilled MCA is prepared containing 1.17 mole percent of iodoform and 1.17 mole percent triiodophenol. The composition also contains 250-750 ppm
5 (mole basis) SO_2 which is added as a stabilizer during the redistillation and sterilization step. About 250 ppm hydroquinone is added to decrease light sensitivity. The mixture is heated with stirring to 80°C for an hour in the dark (a low intensity, dark room type red light may be used). The
10 resulting composition, containing 7 mole percent iodine atoms, may be stored for extended periods in aluminum foil or other containers which are opaque to visible to ultraviolet light. Upon exposure to light, e.g., just prior to use, the composition is stable for two to three hours. When used
15 as female sterilizing agent the polymer plug formed by this composition in the fallopian tube is distinguishable over the pelvic background and an X-ray image.

The fact that this composition is light sensitive, together with the need for heating to completely dissolve
20 the additive materials, suggests that the composition involves a charge transfer complex rather than a single solution of two additives in MCA.

CLAIMS

1. A radiopaque polymerizable cyanoacrylate composition comprising a mixture of an ester of 2-cyanoacrylic acid and a radiopaque additive stable to the cyanoacrylic ester, the additive selected from the group consisting of iodo carboxylic acids; iodo phenols; iodo carboxylic acid esters; iodo methanes; iodo thiophenes; tertiary iodo amines; barium sulfate; bismuth; cadmium tungstate; and calcium tungstate.
2. A composition as claimed in claim 1 in which the additive is:
- a) a primary and secondary amine free, sodium salt free, organic iodo compound;
 - b) barium sulfate;
 - c) bismuth;
 - d) cadmium tungstate; or
 - e) calcium tungstate.
3. A composition as claimed in claim 1 in which the radiopaque additive is:
- 3-acetamido-2,4,6-triiodobenzoic acid
 - acetyl-5-iodosalicylic acid
 - 3,5-diacetamido-2,4,6-triiodobenzoic acid
 - iodamide
 - iodoalphonic acid
 - o-iodohippuratic acid
 - iophenoic acid
 - iothalamic acid
 - 3-[(dimethylaminomethylene)amino]-2,4,6-triiodohydrocinnamic acid

- 3(diacetylamino)-2,4,6-triiodobenzoic acid
2,4,6-triiodo-3,5-dipropionamidobenzoic acid
phenobutiodyl
3,4,5-triiodo-benzoic acid
5 2,3,5-triiodo-benzoic acid
2-(4-hydroxy-3,5-diiodobenzyl)cyclohexane carboxylic acid
3-butyramido- α -ethyl-2,4,6-triiodohydrocinnamic acid
5-iodo-2-oxo-1(2H)-pyridine acetic acid
10 3,5-diiodo-4-oxo-1(4H)-pyridine acetic acid
3-butyramido- α -ethyl-2,4,6-triiodocinnamic acid
3-dimethylamino- α -ethyl-2,4,6-triiodocinnamic acid
N-(3-dimethylamino-2,4,6-triiodobenzoyl)-N-phenyl- β -alanine
15 N,N-dimethyl iocetamic acid
N,N-dimethyl iomeglamic acid
N,N-dimethyl iopanoic acid
tetraiodo phthalic acid
1,4-dihydro-3,5,diiodo-1-methyl-4-oxo-2,6-pyridine
20 dicarboxylic acid
iodophthalein
iocarmic acid
iodipamide
ioglycamic acid
25 alkylesters of said iodo acids;
triiodophenol
tetraiodomethane
iodoform
tetraiodothiophene
30 N-methyltetraiodopyrrole
N-methyl-3,5-diiodo-4(1H) pyridone
barium sulfate
bismuth
cadmium tungstate or
35 calcium tungstate.

4. A composition as claimed in claim 1, 2, or 3 wherein the radiopaque additive is at least partially dissolved in the cyanoacrylate ester.

5. A composition as claimed in claims 1, 2 or 3 wherein finely divided particles of the radiopaque additive are suspended in the cyanoacrylate ester.

5 6. A composition as claimed in any one of the preceding claims wherein the radiopaque additive is present in an amount sufficient to provide an iodine concentration of 4-6 mole percent iodine atoms.

10 7. A composition as claimed in any one of the preceding claims wherein the cyanoacrylate ester is methyl-2-cyanoacrylate.

8. A composition as claimed in any one of the preceding claims wherein the radiopaque additive is an iodo organic acid which also functions as an anionic polymerization inhibitor.

15 9. A composition as claimed in any one of the preceding claims containing a plurality of said radiopaque additives.

10. A composition as claimed in claim 9 wherein the radiopaque additives are triiodophenol and iodoform.

20 11. A composition as claimed in claim 10 wherein the triiodophenol and iodoform are present in approximately equal molar amounts.

25 12. A radiopaque polymerizable composition as claimed in claim 1 comprising a solution in methyl-2-cyanoacrylate of about 1.17 mole percent triiodophenol and about 1.17 mole percent iodoform.

13. A composition as claimed in claim 12 further containing about 250 mole ppm of hydroquinone and sulfur dioxide in a range of about 260-750 mole ppm.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application number

EP 81 30 4706.5

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	FR - A1 - 2 348 699 (HOFFMANN LA ROCHE) * claim 1 *	1,2	C 09 J 3/14 C 09 K 9/02 A 61 K 49/04
A	FR - A1 - 2 352 544 (ROUSSEL-UCLAF) * claim 1 *	1,2	
A,P	Patents Abstracts of Japan Vol. 5, No. 54, 15 April 1981 & JP - A - 56 - 7726	1,3	
P	Chemical Abstracts vol. 94, no. 24, 15 June 1981 Columbus, Ohio, USA W. SZMIGIELSKI et al. "Urogranoic acid as a radiopaque additive to the cyanoacrylic adhesive in transcatheter obliteration of renal arteries" page 353, column 1, abstract no. 197519w & Invest. Radiol. vol. 16, no. 1, 1981 pages 65 to 70	1,3,4, 5	TECHNICAL FIELDS SEARCHED (Int. Cl. 7) A 61 K 49/04 C 07 C 121/413 C 09 J 3/14 C 09 K 9/02
A	Chemical Abstracts vol. 84, no. 20 17 May 1976 Columbus, Ohio, USA W. KUBLAK "Acryl substance for prosthe- tics and implantations" page 361, column 1, abstract no. 140763k & PL - B - 77511	1,3	CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons &: member of the same patent family, - corresponding document
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
Berlin	18-01-1982	KNAACK	